REMARKS

Claims 2, 9, 10, 11, 14, and 21-23 have been cancelled and new Claims 24-48 have been added. Thus, Claims 1, 3-8, 12-13, 15-20 and 24-48 remain presented for examination. No new matter has been added by this amendment. Applicant wishes to thank the Examiner for her examination of the pending claims.

Support for new Claims 24-48 can be found throughout the specification, and particularly on page 7, last paragraph to page 9, second paragraph.

Discussion of Information Disclosure Statement

The Examiner noted that the Gallperin, et al. reference was missing from the parent file at the U.S.P.T.O. Attached herewith is a supplemental Information Disclosure Statement and copy of the Gallperin, et al. reference for consideration.

Discussion of Issues Related to the Oath

The Examiner asserted that a new oath was required as the subject matter claimed in the present continuation application was not originally claimed or presented in Applicant's parent application, U.S. Application number 09/243,022. Applicant respectfully disagrees.

Initially, Applicant notes that the specification of the present application is identical to the specification of the parent patent application. However, the Examiner correctly notes that the claims presented in this continuation application are not identical to the claims originally filed in the corresponding parent application. However, while the pending claims are not identical to the original claims, they are nonetheless fully supported by the present specification, and original claims. Contrary to the Examiner's statements, these claims could have been entered in the parent application without being subject to a new matter rejection.

Claim 1, as originally presented in this continuation application, related to a method of determining a phenotype of an organism by:

> providing a table of metabolic reactions known to take place in the organism, where the products wherein the products of at least one metabolic reaction are linked to the reactants of another metabolic reaction;

determining a candidate metabolic gene on the organism's genome;

providing the nucleotide sequence of the open reading frame of the candidate metabolic gene;

assigning a function to the candidate metabolic gene based on its nucleotide or amino acid homology to other, known metabolic genes;

determining the metabolic reaction of the candidate metabolic gene based on the assigned function of the candidate metabolic gene;

adding the metabolic reaction of the candidate metabolic gene to the table of metabolic reactions; and

determining a phenotype of the organism by performing a mathematical analysis of the table of metabolic reactions.

Claim 32, which was pending in the parent application, and not rejected as containing new matter at the time this continuation was filed, comprised a method for generating a table of metabolic reactions that take place in an organism, comprising:

providing a table of known metabolic reactions in the organism;

determining a metabolic gene whose metabolic reaction in the organism is unknown;

providing the nucleotide sequence of the metabolic gene;

identifying the open reading frame of the metabolic gene;

assigning a function to the metabolic gene based on its nucleotide or amino acid homology to other, known metabolic genes;

determining the metabolic reaction of the metabolic gene based on the assigned function of the metabolic gene; and

adding the metabolic reaction of the metabolic gene to the table of metabolic reactions and further comprising determining a phenotype of the organism based on the table of metabolic reactions.

This claim is very similar to originally filed Claim 2 of the parent application. Accordingly, both Claim 32 from the parent application, and newly filed Claim 1 contained steps of: providing a table of known metabolic reactions, determining an unknown metabolic gene; providing the nucleotide sequence and open reading frame of

the unknown gene; assigning a function to the unknown gene; determining the metabolic reaction corresponding to the unknown gene; adding the metabolic reaction to a table of metabolic reactions, and determining a phenotype of the organism based on the table of metabolic reactions.

These two claims are similar, with the exception that the preamble of pending Claim 1 correctly recites that the method is for determining the phenotype of an organism, based on the last recited step, whereas the preamble of Claim 32 relates to a method of generating a table of metabolic reactions, even though the method comprises determining the phenotype of an organism.

Accordingly, Claim 1 and its dependent claims all relate closely to subject matter that was part of the claims in the parent application as filed. It is axiomatic that the claims of the parent application form part of the application and thus indicate the subject matter which form part of the originally filed application.

Claim 12 of the present application is directed to a computer system that performs the method outlined in pending Claim 1, and Claims 2 and 32 of the parent application. The method steps are identical to the method steps of pending Claim 1, and only differ by the preamble that recites that the method is performed by a computer system having instructions in a memory. The Examiner's attention is drawn to page 6, second full paragraph which states that the methods described in the pending application can be implemented in any conventional host computer system. Paragraph four on page six notes that software normally runs on instructions stored in a memory on the host computer system.

Accordingly, because the method steps recited in Claim 12 as filed were fully supported by Claims 2 and 32 of the parent application, and software methods were described as being run from instructions stored in a memory of a host computer system, Claim 12 is entitled to the February 2, 1999 priority of the parent application.

For all of the above reasons, Applicant respectfully requests that the Examiner reconsider her requirement for a supplemental oath and explicitly grant Applicant priority to the February 2, 1999 filing date of the parent application for this continuation application.

Discussion of the Objection to the Specification

The Examiner objected to the specification as not providing the proper antecedent basis for the claimed subject matter for a variety of reasons. Applicant respectfully traverses.

Alleged Lack of Disclosure

As one part of the objection, the method and computer system for determining a phenotype of an organism was argued to not be shown in the specification. Applicant disagrees. Throughout the specification, Applicant has described a system and method for generating a table of metabolic reactions (a metabolic genotype) that can be used to determine an organism's phenotype, such as growth. In addition, beginning on page 6, second full paragraph, Applicant states that the methods described in the pending application can be implemented in any conventional host computer system. Paragraph four on page 6 notes that software normally runs on instructions stored in a memory on the host computer system.

For example, on page 15, Applicant provides a description of an actual experiment wherein metabolic genes involved in growth of *E. coli* were analyzed as potential antimicrobial targets. Thus, Example 2 provides a description of a method for determining a phenotype (growth) of an organism (*E. coli*).

Example 2 first points out that Applicant created an *in silico* strain (table of metabolic reactions) by the method of Example 1. An example of a metabolic table can be found in Table 1, which shows *E. coli* metabolic reactions, including reactants and products. As described, the model of *E. coli* was generated from annotated sequence data and biochemical information. Genetic sequence and open reading frame assignments were made from the annotated sequence data. Accordingly, the specification fully supports the claims, and withdrawal of this objection is respectfully requested.

Claim 16

Applicant has amended Claim 16 to remove the duplicated period. Accordingly, withdrawal of this rejection is respectfully requested.

Hyperlink

Applicant has amended the specification to remove reference to hyperlinks. Accordingly, withdrawal of this rejection is respectfully requested.

Figure 2

The Examiner correctly noted that Figure 2 inadvertently did not contain the number "50" which referred to the overall process illustrated in that figure. Applicant submits herewith a substitute Figure 2, with the addition of the reference numeral 50. Introduction of the number 50 does not add new matter, as it is clear from the specification that the number 50 refers to the overall process indicated in Figure 2.

Discussion of Rejections Under 35 U.S.C. § 112, first paragraph

The Examiner rejected Claims 1-23 under 35 U.S.C. § 112, first paragraph, as not enabling one of ordinary skill in the art to make and use the invention. Applicant respectfully disagrees.

As stated in *In re Wands*, enablement requires that one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. There is no requirement that to be enabling, the specification must disclose only operative embodiments. The court in *In re Wands* held that, in an application for immunoassay methods using a generic class of antibodies, the applicants' specification was sufficiently enabling even though the data indicated that not all hybridoma fusions were successful. The court stated that practitioners in the art are prepared to screen negative hybridomas in order to find one that makes the desired antibody, and therefore only routine experimentation was required to practice the claimed invention.

The Examiner argued that Applicant did not enable methods of determining a phenotype, but only describe methods for determining a *metabolic* phenotype. Applicants disagree, however have clarified the language of the claims to recite that a metabolic phenotype is determined.

In addition, the Examiner remarked that the Claims did not recite the particular mathematical analysis to be performed. Applicant traverses this rejection, and argues that one of ordinary skill in the art would be able to determine a metabolic phenotype using a variety of

mathematical methods. However, solely to advance prosecution of this application, Applicant has amended the Claims to recite that the step of determining a phenotype of the organism includes performing a flux balance analysis on the table of metabolic reactions, as described throughout the specification. *See* page 11, second paragraph. In addition, on page 13 of the specification, Applicant sets forth a description of determining metabolic phenotypes by adding and removing constraints to a table of metabolic reactions and then analyzing those constraints with a flux balance analysis.

> "Thus, by adding or removing constraints on various fluxes in the network it is possible to (1) simulate a genetic deletion event and (2) simulate or accurately provide the network with the metabolic resources present in its *in vivo* environment. Using flux balance analysis it is possible to determine the affects of the removal or addition of particular genes and their associated reactions to the composition of the metabolic genotype on the range of possible metabolic phenotypes. If the removal/deletion does not allow the metabolic network to produce necessary precursors for growth, and the cell can not obtain these precursors from its environment, the deletion(s) has the potential as an antimicrobial drug target. Thus by adjusting the constraints and defining the objective function we can explore the capabilities of the metabolic genotype using linear programming to optimize the flux distribution through the metabolic network. "

Accordingly, Applicant teaches that a flux balance analysis can be used to determine the affects of the removal or addition of particular genes, and their associated reactions to the composition of the metabolic genotype on the range of possible metabolic phenotypes. For this reason, the specification fully enables one of ordinary skill in the art determine a metabolic phenotype using a flux balance analysis of the table of metabolic reactions.

The Examiner also argued that assigning a function to a candidate gene would not necessarily provide the metabolic reaction of that gene. As an example, the Examiner stated that the assignment of a kinase function to an unknown gene would not necessarily provide the substrate and product of the kinase reaction for that gene. Applicant points out that it may not be possible, in every single case, to determine the products and reactants for an unknown gene through a homology-based functional assignment. However, in many cases it is possible to assign the products and reactants of a reaction once a function has been assigned to a particular gene. Moreover, as recited in *Wands*, inoperable embodiments are permitted. Thus, it is

certainly not required for Applicant to enable determination of reactants and products for *every* unknown gene in the organism. It is sufficient that Applicant has taught that functional assignment actually works to assign reactants and products, and to create metabolic genotypes for determining metabolic phenotypes, as fully described in the present specification.

In addition, as evidence that it would not require undue experimentation to generate a table of metabolic reactions by assigning a function to unknown genes through homology matching, with metabolic genes of a known function, Applicant has previously submitted in parent application 09/243,022 two articles written by the inventor of this application (The *Escherichia coli* MG1655 *in silico* metabolic genotype: Its definition, characteristics, and capabilities, *Proc. Natl. Acad. Sci.*, **97(10):** 5528-5533 (2000) and Systems Properties of the *Haemophilus influenza* Rd Metabolic Genotype, *J. Biol. Chem.* **274(25):** 17410-17416 (1999)). These articles were published after the effective priority date of the present application and are thus not prior art.

These articles describe generation of metabolic genotype tables for *Escherichia coli* and *Haemophilus influenza* using the methods described in the instant application. In addition, the metabolic phenotype of growth is illustrated for each of these organisms. For example, each article describes using the annotated gene sequence from each organism to construct a functioning metabolic genotype. Accordingly, one of ordinary skill in the art could follow the teachings of the specification, as was done in the cited articles, to construct a functioning table of metabolic reactions in order to study metabolic phenotypes of an organism.

Similarly, practitioners in the art are prepared to perform homology matches for a metabolic gene of unknown function until the proper function has been assigned. Such experimentation would only be routine and not undue. Moreover, the claims do not require the determination of *every* metabolic reaction in the organism by functional assignment. In contrast, the claims recite that a table of metabolic reactions *known to take place in the organism* is first provided. Once the table of *already* known reactions is provided, a functional assignment is made for genes that are still unknown.

Accordingly, the claimed methods are enabled because "merely routine" testing would be required of a skilled artisan armed with Applicants' roadmap for performing homology searches against databases of genes with assigned functions. As stated in *Wands* "[A] considerable amount

of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In this case, the specification provides sufficient guidance so that one of ordinary skill in the art could make a functional assignment of an unknown gene and then add that gene to a table of metabolic reactions. Even if the initial functional assignment was incorrect, one of ordinary skill in the art could perform additional homology matches to determine the correct functional assignment so that the table of metabolic reactions functioned in a manner consistent with the organism it was representing. For all of these reasons, Applicant respectfully requests withdrawal of the enablement rejection.

The Examiner rejected Claims 2 and 14 as being indefinite for failing to limit the scope of their independent claims. Applicants have cancelled Claims 2 and 14, thus obviating this rejection.

Discussion of Rejections Under 35 U.S.C. § 102

The Examiner rejected Claims 1-23 as being obvious in view of Edwards, et al. However, as discussed above, Applicant is entitled to their original filing date of February 2, 1999. As Edwards, et al. was published after this date, it is not prior art under 35 U.S.C. § 102. For this reason, Applicant respectfully requests withdrawal of this rejection.

Applicant has endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. Any claim amendments which are not specifically discussed in the above remarks are made in order to improve the clarity of claim language, to correct grammatical mistakes or ambiguities, and to otherwise improve the capacity of the claims to particularly and distinctly point out the invention to those of skill in the art. In light of the above amendments and remarks, reconsideration and

withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: April 15, 2003

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